5. By the Van Slyke method the normal CO_2 capacity of the plasma reduced to 0° 760 mm. pressure and correcting for vapor tension appears to be about sixty-five to eighty volumes per cent. This is slightly reduced in arteriosclerotic conditions and moderately to markedly reduced in diabetes and nephritis, especially in the advanced stage.

6. After ether anesthesia there is a depression of the CO_2 capacity of the plasma of from two to twenty volumes per cent. This depression is proportional to the duration of the anesthesia. The lowest figure observed was 47. This reduction is present and probably maximal at the close of the anesthesia, and apparently remains little altered for at least five hours. A single injection of two pints of a 5 per cent. glucose solution per rectum at the close of the anesthesia does not lessen the reduction in the CO_2 capacity during the next five hours.

THE TOXEMIAS OF PREGNANCY.

By J. R. Losee, M.D.,

and

Donald D. Van Slyke, Ph.D.,

NEW YORK.

(From the Lying-in Hospital and the Hospital of the Rockefeller Institute for Medical Research, New York.)

Although no general agreement has been reached concerning the nature of the substances causing the toxemias of pregnancy, two explanations have claimed special consideration. Ewing and Wolf,[1] noting the anatomical changes of the liver in eclampsia, the facts that leucine and tyrosine had been reported in eclamptic urines, and that they themselves found often a decrease in urea and an increase in the "undetermined nitrogen" fraction of the urine, suggested that the amino-acids were incompletely catabolized in the degenerated liver, and were the cause of both the toxemia and the abnormal nitrogen distribution. Later Murlin and Bailey,[2] also working in the Cornell laboratory, attacked the same problem with the aid of Soerensen's formol titration method, which is specific for amines and amino-acids. They decided that not only the amino-acid fraction, but also the other nitrogen fractions of the urine are likely to be within the limits of normal variation both before and immediately after the convulsions of eclampsia, and that consequently the nitrogen distribution in the urine offers no reliable

[1] Am. Jour. Obst., 1906, lv, 289.
[2] Jour. Am. Med. Assn., 1912, lix, 1522.

means for either diagnosing the preëclamptic state or indicating the nature of the toxin.

The other explanation is that abnormal acids in the blood are responsible for the toxemia. It is known that even in normal pregnancy a slight degree of acidosis is indicated by the carbon dioxide content of the alveolar air,[3] and it was not illogical to suggest that an intensification of the acidosis might be a factor in the cause of eclampsia. Zweifel[4] not only designated acidosis as the cause of eclampsia, but identified the specific acid as sarcolactic. This he found to be three times as concentrated in blood from the umbilical cord as in the venous blood of the mother, and he interpreted the results as proof that the mother is intoxicated by lactic acid formed in the fetus. Hasselbalch and Gammeltoft[5] found also that in two out of four cases of eclampsia examined by them the "regulated" hydrogen ion concentration of the blood was abnormally high, the values for pH at normal CO_2 tension being 7.17 and 7.22 instead of the normal 7.45.

It seemed to the writers desirable to test the acidosis hypothesis quantitatively on a number of cases in order to ascertain whether a degree of acidosis unusual for pregnancy regularly accompanies eclampsia, and whether the intensity of the acidosis is sufficient to account for the symptoms and ultimate coma noted. It seemed also not without interest to test with the gasometric method the proportion of amino-acid nitrogen in the urine in eclampsia, since the results of previous investigations on amino-acids in the urines of pregnancy, which have been performed with the help of the formol titration method, have not been entirely in agreement. While Hasselbalch and Gammeltoft found the proportion of amino-acid nitrogen normal (2 to 3 per cent. of the total nitrogen) in normal pregnancy, Falk and Hesky, with the same method, report results running chiefly between 3 and 7 per cent., 73 per cent. of the cases showing figures above the ordinary limits observed in non-pregnant women. Falk and Hesky also noted in pregnancy a similar increase in peptide nitrogen, which varied from 2 to 7 per cent., non-pregnant women showing figures of from 1 to 2 per cent. Murlin and Bailey did not determine the peptide nitrogen, but found in their three cases of normal pregnancy amino-acid nitrogen figures of 3.3, 5.1, and 4.3 per cent. of the total nitrogen, figures which, like those of Falk and Hesky, are somewhat above the normal.

We have determined in the urine the "total amino-acid nitrogen,"[6] which includes the nitrogen of the free amino-acids and also that of the amino-acids conjugated in such forms as peptides and hippuric acid. In normal individuals this nitrogen runs from 1.5 to

---

[3] Hasselbalch, K. A., and Gammeltoft, S. A., Biochem. Ztschr., 1915, lxviii, 207.

[4] München. med. Wchnschr., 1906, liii, 297.

[5] Loc. cit.

[6] Levene, P. A., and Van Slyke, D. D., Jour. Biol. Chem., 1912, xii, 310; 1913, xvi, 125.

3.5 per cent. of the total nitrogen. Consequently the excretion of any considerable amount of amino-acids either free or conjugated would cause a marked rise in this figure. We have also determined the proportion of the total nitrogen in the form of urea, ammonia, and albumin.

As a further index of the amino-acid metabolism we have determined in a number of cases the amino-acid nitrogen of the blood[7] since the blood can be expected, even before the urine, to show evidence of failure of the organism to metabolize amino-acids with normal efficiency. The total non-protein nitrogen and urea nitrogen were also determined in most of the blood analyses.

As a measure of acidosis we have determined the volume percentage of carbon dioxide bound in the form of bicarbonate by the blood plasma.[8] Since all the reserve alkali of the blood, *i. e.*, the alkali in excess of that combined with acids other than carbonic, takes the form of bicarbonate, this figure indicates the alkaline reserve of the blood plasma, and in fact of the body as a whole.

METHODS. Urea was determined in both blood and urine by Marshall's urease method in the form developed by Van Slyke and Cullen.[9]

Amino-acid nitrogen of the blood was determined after precipitation of the proteins by alcohol, as described by Van Slyke and Meyer.[10] The micro-amino apparatus was used, so that the determinations could be done on an amount of filtrate corresponding to 2 c.c. of blood. As shown by Greenwald[11] the proteins precipitated by alcohol adsorb a portion of the amino-acid nitrogen, but the proportion is so constant that for comparative purposes the method is accurate.

Total non-protein nitrogen of the blood was determined by Folin micro-Kjeldahl[12] determination on an aliquot portion of the alcoholic filtrate from the blood proteins.

Carbon dioxide capacity of the plasma was determined by Van Slyke's method.[13]

The albumin of the urine was determined by a modification of Welker's method[14] as follows: Twenty-five c.c. of urine were acidified with acetic acid and heated to coagulate the albumin. The volume of the solution was then brought to 50 c.c. by the addition of an aluminum hydroxide suspension, prepared as described by Welker for adsorption of proteins, and containing 0.5 per cent. of Al_2O_3. The mixture was shaken and filtered through a folded filter. The nitrogen content was determined by Kjeldahl on 4 c.c. of the filtrate and on 2 c.c. of the untreated urine. The difference indicated the albumin nitrogen.

---

[7] Van Slyke, D. D., and Meyer, G. M., Jour. Biol. Chem., 1912, xii, 399.

[8] Van Slyke, D. D., Proc. Soc. Exper. Biol. and Med., April 21, 1915.

[9] Jour. Biol. Chem., 1914, xix, 211.

[10] Loc. cit.

[11] Jour. Biol. Chem., 1915, xxi, 61.

[12] Jour. Biol. Chem., 1913, xi, 529.

[13] Loc. cit.

[14] Tracy, G., and Welker, W. H., Jour. Biol. Chem., 1915, xxii, 55.

The use of the aluminum hydroxide alone, without previous coagulation of the mass of the albumin, proved insufficient to remove all the albumin from some of the urines in which it was especially abundant.

The total amino-acid nitrogen of the urine was determined on 25 c.c. of the albumin-free filtrate by the gasometric method previously described, the urea being destroyed and conjugated amino-acids set free by heating with dilute sulphuric acid in an autoclave.

The *ammonia* was determined by Folin's aëration method, 5 c.c. of saturated potassium carbonate solution being added to 5 c.c. of urine, and the ammonia aërated into 0.02 N hydrochloric acid.

DISCUSSION OF RESULTS. *Acidosis.* Examination of between 20 and 30 normal plasmas by Van Slyke, Stillman, and Cullen,[15] and of 30 by Gettler and Baker[16] have shown that 100 c.c. of average normal plasma binds 65 c.c. of CO_2, no normal plasma showing a figure below 55 and very few above 75, the great majority lying in the range 60 to 70. Our 14 cases of normal pregnancy all showed figures below the average normal of 65, and 10 of them were observed on at least one day to show figures below the minimum normal of 55. Consequently we can agree with the conclusion reached as the result of their alveolar carbon dioxide determinations by Hasselbalch and Gammeltoft,[17] that a slight acidosis is usually present in even normal pregnancy.

Our cases of toxemia of both the eclamptic and vomiting type show little difference from normal pregnancy in their alkaline reserve. The same subnormal carbon dioxide is seen, but in no case does it approach so low a value as 30 c.c. of CO_2 per 100 c.c. of plasma, which experience with the acidoses of diabetes and nephritis indicates must be fallen below, before any but exceptional cases show serious distress from acidosis *per se.*

The blood from the umbilical cord showed a bicarbonate content in only one case significantly different from that of the mother's blood. The results give no support to the presumption that the fetus elaborates amounts of acid sufficient to cause acidosis in the mother.

It is noteworthy that although the cases of pernicious vomiting show strikingly high ammonia figures, the plasma bicarbonate indicates no greater degree of acidosis than may be observed in non-toxic pregnancy. A. W. Sellards[18] mentions similarly a case of toxemia of pregnancy in which 40 per cent. of the urinary nitrogen was ammonia, but in which other evidence excluded acidosis.

---

[15] Loc. cit.
[16] Jour. Biol. Chem., 1916, xxv, 211.
[17] Loc. cit.
[18] Johns Hopkins Hosp. Bull., 1914, xxv, 147.

Amino-acids. In only 3 of the 23 cases of toxemia in which amino nitrogen of the urine was determined was the figure above the 3.6 per cent., the maximum noted in a previous series of normal men. In the 3 cases where a higher figure was observed the amino nitrogen exceeded the usual limit by a margin smaller that the maxi-

TABLE I.—PLASMA BICARBONATE AND NITROGEN DISTRIBUTION OF URINE IN NORMAL PREGNANCY.

History.	Total N.	Urine.					C.c. of CO_2 bound by 100 c.c. of plasma.	
		Per cent. of total N. as:						
Para, months pregnant, etc.	g. per 100 c.c.	Albumin.	Urea.	Ammonia.	Total amino-acids.	Undetermined.	Mother's blood.	Infant's blood.
Full term	1.168	..	75.8	5.8	..	..	57	
Full term	1.014	..	83.8	5.8	3.7	6.7	60	
2 days p. p.	0.782	..	83.2	4.4	2.6	9.8	54	
Full term	0.596	..	69.2	7.0	5.4	18.4	51	
1 day p. p.	0.963	..	75.8	6.7	3.7	13.8	61	
Full term;	..	..	..	..	..	..	53	51
2d blood; 2 days p. p.							54	
Full term;	..	..	..	..	..	..	51	56
2d blood; 3 days p. p.							62	
Full term;	..	..	..	..	..	..	49	52
2d blood; 3 days p. p.							58	
Full term;	..	..	..	..	..	..	50	53
2d blood; 3 days p. p.							63	

TABLE II.—NITROGEN DISTRIBUTION OF BLOOD AND URINE IN ECLAMPSIA.

History.	Non-protein N. of blood. Mg. per 100 c.c.			Urine.					
				Total N.	Per cent. of total N. as:				
Para, months pregnant, blood-pressure, etc.	Total.	Urea.	Amino acids.	g. per 100 c.c.	Albumin.	Urea.	Ammonia.	Total amino acids.	Undetermined.
P. V, 8 mos., 230 b. p.; accouchment force; died, typical liver lesions	46	21	7.6	0.642	4.7	54.3	10.2	2.5	25.7
P. I, 8 mos., 248 b. p.; no convulsions nor coma; mild type	36	14	7.9	1.410	6.2	64.4	8.1	2.7	17.6
P. IV, 9 mos., 196 b. p.; semicomatose 7 days; died 5 days p. p.	31	10	7.9	0.784	20.9	46.1	3.1	3.2	26.7
P. I, 9 mos., 140 b. p.; semicomatose	26	15	4.0	0.610	10.1	56.2	3.2	2.5	28.0
P. I, 8 mos., 170 b. p.; marked edema	28	..	6.2	0.374	17.9	62.0	6.6	2.0	11.5
P. I, 7 mos., 170 b. p.; edema	25	..	7.8	1.195	4.1	66.2	10.1	2.3	17.3
P. I, 9 mos., 180 b. p.; no convulsions	28	..	5.0	0.633	16.3	51.2	10.2	3.1	19.2
P. I, 8 mos., 150 b. p.; died in coma, 6 days p. p.; first urine and blood 4 days p. p.; second 5 days p. p.	43	26	4.4	1.887 2.275	1.1 7.7	74.0 72.0	5.6 4.6	2.0 1.5	17.3 14.2
P. I, 9 mos., 125 b. p.; moderate edema; coma; first specimen day of delivery; second one day p. p.	41 41	25 26	5.5 4.3	0.680 0.795	9.7 1.9	53.0 74.5	12.0 7.4	4.7 3.5	20.6 12.7
P. I, 8 mos., 165 b. p.; edema; general condition fair	32	11	5.0	0.383	24.3	49.3	6.0	2.5	17.9

mum observed either by K. W. Wilson[19] or ourselves in normal pregnancy. The results confirm those obtained by Murlin and Baily with the formol method.

Not a single one of the 10 eclamptic women whose blood was examined for amino nitrogen showed a figure outside the range

TABLE III.—PLASMA BICARBONATE AND NITROGEN DISTRIBUTION OF URINE IN ECLAMPSIA.

History.	Total N. g. per 100 c.c.	Urine.					C.c. of CO_2 bound by 100 c.c. of plasma.	
		Per cent. of total N. as:						
Para, months pregnant, b. p., etc.		Albumin.	Urea.	Ammonia.	Total amino-acids.	Undetermined.	Mother's blood.	Infant's blood.
P. I, 9 mos., 168 b. p.; convulsions	0.554	15.3	57.3	8.1	..	..	52	
P. I, 9 mos., 186 b. p.; blood and urine 48 hours p. p.; coma	1.595	..	..	..	2.6	..	54	
P. II, 24 hrs. p. p., 170 b. p.; eight convulsions; p. p. eclampsia	0.706	1.6	68.5	8.9	2.6	18.4	47	
P. III, 10 hrs. p. p.; 170 b. p.; p. p. eclampsia	0.530	29.2	..	7.9	1.6	..	46	
P. I, 8 mos., 186 b. p.; semicomatose; convulsions; blood 14 hrs. p. p.; urine 30 hrs. p. p.	1.090	3.2	65.7	7.4	2.5	21.2	45	
P. III, 7 mos., 220 b. p.; convulsions and edema	1.025	54.7	27.2	8.3	4.1	5.7	45	
P. VI, 9 mos., 160 b. p.; convulsions; blood and urine 2 days p. p.	0.449	+	75.9	4.5	2.2	17.4	58	
P. I, 8 mos.; convulsions; coma	0.639	Trace	63.3	11.3	4.6	20.8	43	47
P. III, 5 days p. p., 168 b. p.; p. p. eclampsia and convulsions	0.674	25.5	53.1	2.0	2.9	16.5	51	
P. I, 9 mos., 216 b. p.; no convulsions; first specimen one day before delivery; second labor day	0.215	+	56.8	6.0	..	..	47 41	 32
P. I, 5 mos., 190 b. p.; preëclamptic	..	..	..	..	..	..	54	
P. ——, 9 mos., 156 b. p.; semicomatose; convulsions	..	..	..	..	..	..	45	47
P. I, no convulsions; edema	..	..	..	..	..	..	47	45
P. I, 8 mos., 156 b. p.; coma	..	..	..	..	..	..	44	

TABLE IV.—PLASMA BICARBONATE AND NITROGEN DISTRIBUTION OF URINE IN PERNICIOUS VOMITING.

History.	Urine.						C.c. of CO_2 bound by 100 c.c. of plasma.
	Total N. g. per 100 c.c.	Per cent. of total N. as:					
Para, months pregnant, b. p., etc.		Albumin.	Urea.	Ammonia.	Total amino-acids.	Undetermined.	Mother's blood.
P. I, 3 mos., 140 b. p.; vomiting two weeks; much emaciated	0.782	1.5	54.8	24.9	2.4	16.4	
P. II, 3 mos.; vomiting one week	1.020	..	46.3	31.2	2.3	..	62
3 months	0.602	..	55.4	27.4	2.3	14.9	
2½ months	1.645	..	67.4	17.5	2.2	12.9	52
3 months	1.791	..	64.1	16.9			
P. II, 2½ mos.; vomiting four weeks; condition bad	0.928	Trace	51.1	29.0	2.9	17.0	41

---

[19] Johns Hopkins Hosp. Bull., 1916, xxvii, 121.

4 to 8 mg. per 100 c.c. noted by Ellis, Cullen and Van Slyke[20] in a series of normal men. In brief, neither blood nor urine of eclamptic women shows, as a rule, an amino-acid content above normal limits.

Inspection of the other nitrogen figures of the urine shows that the *urea in eclampsia* is usually below the average normal, often strikingly so, even if calculated on the basis of total nitrogen of the urine minus the albumin nitrogen. The only eclamptic urines which showed more than 70 per cent. of urea nitrogen were those obtained one or more days postpartum. The ammonia was often higher than the average in normal individuals, but the abnormality is less striking than that of the urea. The ammonia and urea ratios are suggestive of those which Nencki and Pavlov[21] obtained from dogs from which the livers had been removed.

All the cases of *pernicious vomiting* showed strikingly *high ammonia* percentages. It appears quite possible that this fact may be due, as pointed out by Underhill and Rand,[22] merely to fasting, and that Williams'[23] separation of pernicious vomiting cases into those of toxic and nervous origin, according as the urinary ammonia is high or low, is not justified. Regardless of its etiological significance, however, the frequency of the appearance of high ammonia in pernicious vomiting (none of our 6 cases showed less than 16.9 per cent.) must be admitted to give to the ammonia ratio an undoubted diagnostic value.

The above findings concerning the ammonia and urea ratios in eclampsia and pernicious vomiting confirm the results of Ewing and Wolf.[24]

In our 5 cases of non-toxic pregnancy the nitrogen ratios were normal.

CONCLUSIONS.—The toxemias of pregnancy can be attributed neither to failure in diaminization of the amino-acids, nor to the moderate degree of acidosis observed. The nature of the toxin or toxins therefore remains unknown.

The nature of the functional disturbances which cause the abnormal nitrogen metabolism observed also still awaits a satisfactorily conclusive explanation. Nevertheless the constancy of the low urea ratios in the urine in eclampsia, and of high ammonia in pernicious vomiting, lends decided support to the opinion of Ewing and Wolf, that the nitrogen distribution of the urine, considered "in connection with all the data in the case," should assist in diagnosing the toxemias of pregnancy, and in differentiating them from conditions such as nephritis and transitory gastric disorders.

---

[20] Jour. Am. Med. Assn., 1915, lxiv, 126.

[21] Arch. f. exper. Path. u. Pharmakol., 1897, xxxviii, 215.

[22] Arch. Int. Med., 1910, v, 61.

[23] Johns Hopkins Hosp. Bull., 1906, xvii, 71.

[24] Loc. cit.